

### REMARKS

Claims 1, 3-13, and 28 are pending.

Claims 1, 3-9, and 28 remain rejected under 35 U.S.C. § 102(b) over McAuliffe et al., J. Gastrointest. Surg. 4:580-588, 2000, as evidenced by Alemany et al., U.S. Patent No. 6,403,370.

Claims 1, 3-13, and 28 remain rejected under 35 U.S.C. § 103(a) for obviousness over Alemany, in view of McAuliffe.

Claims 1, 3-6, 8-13, and 28 remain rejected under 35 U.S.C. § 102(e) as being anticipated by Fong et al., US 2002/0071832.

Claims 1, 6, and 7 remain rejected under 35 U.S.C. § 103(a) for obviousness over Fong et al., US 2002/0071832, in view of Wong et al., Human Gene Therapy 12:253-265, 2001.

The rejections are addressed as follows.

First, Applicants note that claim 1 has been amended to specify that the cancer is present in the lymphatic system of the subject, as originally specified in claim 4, which has been canceled. In addition, claims 1 and 28 have been amended to include a step of identifying a patient at risk for or having lymphatic metastasis. Support for this amendment can be found throughout the application, for example, in the experiments and paragraph 3 of the specification. No new matter has been added.

#### *Rejection over McAuliffe and Alemany*

The Examiner states that the process described by McAuliffe provides “guidance for administering virus to a tumor bed to a patient with metastatic cancer.” (Current Office action, pg 3). However, the Examiner does not cite, nor do we find, any description in McAuliffe that would teach or suggest the treatment of metastatic cells by administering oncolytic HSV as claimed. Indeed, the experiments of McAuliffe only involve injection of tumors, not application of virus to resection sites (page 582 of McAuliffe).

While the Examiner argues that one skilled in the art at the time of the invention, based on the teaching of Alemany, would have recognized that the procedures taught by McAuliffe *could* have been used to treat metastasis (Current Office action, pg. 4), nothing in Alemany indicates that the procedures disclosed by McAuliffe actually resulted in the treatment of

metastatic cancer. In order to anticipate the claims, the teachings of McAuliffe would have had to, in fact, describe the treatment of metastasis. Whether one skilled in the art would have found it obvious to use the virus of McAuliffe to treat metastasis based on Alemany is a determination of obviousness under 35 U.S.C. § 103(a). The rejection of the current claims for obviousness over Alemany, in view of McAuliffe is addressed below.

Further, we refer the Examiner to the Declaration of Yuman Fong submitted on February 20, 2009 in this case. Dr. Fong is an inventor named on the present application, as well as the cited Fong reference (see below). Dr. Fong also is the senior author on the McAuliffe reference, and he is an expert in this field. In regard to the cited Fong reference, Dr. Fong states in the declaration that the purpose of administration of an oncolytic herpes virus to the site of surgical resection of a tumor “is to kill any residual tumor cells that may exist at the resection site, and not to treat metastases at a site distal to the resection site.” This description in Fong is similar to the suggestion in McAuliffe to apply virus to a resection site to destroy residual tumor cells. Dr. Fong’s testimony on what such a teaching means to those skilled in the art should be given considerable weight in determining the relevance of the teaching of McAuliffe (and the cited Fong reference), particularly as senior author of the reference.

While Applicants do not concede that McAuliffe inherently anticipates the claimed invention, in the interest of expediting prosecution, Applicants have amended claim 1 to include a step of identifying a subject having or at risk of developing lymphatic metastasis. McAuliffe teaches experiments conducted in mouse models to kill pancreatic tumor cells. McAuliffe also contains a brief paragraph in the discussion suggesting the possibility that oncolytic HSV could be used to kill tumor cells remaining in the resection bed after a tumor is resected. However, nowhere does McAuliffe teach a method of identifying a subject having or at risk of developing lymphatic metastasis and resecting a primary tumor, followed by administration of oncolytic HSV to treat lymphatic metastasis. Alemany does not provide evidence that McAuliffe inherently identified subjects at risk for developing lymphatic metastasis. Therefore, the rejection of claims 1, 3-9, and 28 as being anticipated by McAuliffe, in view of Alemany, can be withdrawn.

*Rejection over Alemany et al. in view of McAuliffe et al.*

Claims 1, 3-13, and 28 were rejected for obviousness over Alemany in view of McAuliffe. The Examiner states that Alemany teaches “propagation of the [virus] in the tumor cells results in lysis of the tumor cells and generate a local tumorcidal effect and a systemic antitumoral response that results in rejection of distant metastasis.” (Office action dated May 13, 2009, pgs. 9-10). The Examiner further states that it would have been obvious in view of McAuliffe to modify the teachings of Alemany to utilize an oncolytic HSV.

As an initial matter, Applicants submit that the term “resection” as used in the claims means in the view of the surgeon that he intends to remove the complete tumor. Throughout the specification, the administration of virus is always to the site of resection of the tumor (where residual tumor cells might be present), not to a partially intact tumor as described by Alemany (see, e.g., “[i]n the methods of the invention, a tumor is surgically removed from a subject and the site of the resection is treated with an attenuated, replication competent, oncolytic herpes virus,” paragraph 0016 of the specification). Therefore, as submitted previously, the method taught by Alemany requiring at least some tumor cells left at the injection site teaches away from the claimed method of administering an oncolytic virus to a tumor resection bed.

Furthermore, modifying the teachings of Alemany of treating intact (or surgically debulked) tumors with oncolytic virus, in order to treat the tumor bed of a resected tumor as suggested by McAuliffe, would render the teachings of Alemany unsatisfactory for its intended purpose. As provided by M.P.E.P. § 2143.01(V), “if proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification.”

As previously submitted, Alemany teaches the administration of oncolytic virus to an intact or surgically debulked tumor in order to allow “propagation of the [virus] to lyse the tumor cells and further carry on the infection in neighbor cells as well as generate an immune response. The continuous local tumorcidal effect leads to a systemic antitumoral response that involves rejection of distant metastases (FIG. 12).” (Col. 21, ln 15-20; Emphasis added). Therefore, according to Alemany, it is a critical feature that the tumor remains partially intact in order to generate enough tumor cell death in order to trigger a systemic immune response. McAuliffe

suggests administration of the virus to “viable tumor cells present in the resection bed” when “there may be viable tumor cells present in the resection bed but the tumor cell burden is low.” (McAuliffe pg. 586; emphasis added). Therefore, one skilled in the art at the time of the invention would not have expected the treatment of cells present in the resection bed after complete removal of the tumor to induce the systemic immune response necessary to treat metastasis, according to Alemany, because a “continuous local tumoricidal effect” is, based on Alemany, necessary to achieve a systemic immune response. Because the Examiner has proposed a modification to Alemany, based on McAuliffe, that would render Alemany unsatisfactory for its intended purpose, the rejection for obviousness should be withdrawn.

*Rejection over Fong et al., US 2002/0071832*

The Examiner also rejects claims 1, 3-6, 8-13, and 28 as being anticipated by Fong. Similar to McAuliffe, Fong does not teach the treatment of lymphatic metastasis using an oncolytic HSV. The Examiner states that, in view of Alemany, one skilled in the art at the time of the invention would have known “that using oncolytic virus was a way of treating metastatic cancer in Fong et al.’s teaching.” (Current Office action, pg. 8). However, in order to anticipate the claims, the teachings of Fong would have had to, in fact, described the treatment of metastasis. Whether one skilled in the art would have found it obvious to use the methods of Fong to treat metastasis based on Alemany is a determination of obviousness under 35 U.S.C. § 103(a).

While Applicants do not concede that Fong inherently anticipates the claimed invention, Applicants have amended claim 1 to include a step of identifying a subject having or at risk of developing lymphatic metastasis. Fong teaches administration of oncolytic HSV to a tumor bed in order to kill residual tumor cells. However, nowhere does Fong teach a method of identifying a subject having or at risk of developing lymphatic metastasis and resecting a primary tumor followed by administration of oncolytic HSV to treat lymphatic metastasis. Alemany does not provide evidence that Fong inherently identified subjects at risk for developing lymphatic metastasis. Therefore, the rejection of claims 1, 3-6, 8-13, and 28 for anticipation can be withdrawn.

Lastly, the Examiner has rejected claims 1, 6, and 7 over Fong in view of Wong et al. Wong was cited by the Examiner as teaching the specific viral strain of NV1023. Neither Wong nor Fong teach a step of identifying a subject having or at risk of developing lymphatic metastasis. Therefore, the combination of Wong and Fong do not render the claimed subject matter obvious and this rejection should be withdrawn. Further, Applicants submit herewith a Statement of Common Ownership, which provides that Fong and present application were commonly owned at the time that the present application was filed. Fong is therefore removed as a reference under 35 U.S.C. § 102(e)/103(a) pursuant to 35 U.S.C. § 103(c).

CONCLUSION

Applicants submit that the claims are in condition for allowance, and such action is respectfully requested. Please apply any charges not covered or any credits to Deposit Account No. 03-2095.

Respectfully submitted,

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